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ABSTRACTS

The Depressing Effect of Inositol on Serum Cholesterol and Lipid Phosphorus in Diabetics

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Inositol, an essential vitamin and a lipotropic factor, has been reported to have a specific effect on cholesterol metabolism and to lower elevated levels of blood lipids. The relation of inositol to cholesterol metabolism is being studied at this hospital.

Thirty adequately controlled diabetic patients were selected at random from the diabetic clinic. Serum cholesterol, cholesterol esters and lipid phosphorus were determined on all subjects. When compared with a group of 100 normals, 18 (60%) of the diabetic group were found to have lipid levels above the range of normal.

The diabetics were then given inositol by mouth in doses of one gram three times a day for a period of eight weeks. All patients had a drop in the level of the measured serum lipids. The major portion of the drop usually occurred in the early weeks of administration. The higher the initial levels, the greater was the tendency to fall. At the end of eight weeks, all determinations were within the range of normal. The mean total cholesterol fell from 294 mgms. per cent to 244 mgms. per cent (normal=237 mgms per cent).

Preliminary results in a group of patients with arteriosclerotic heart disease would seem to indicate that inositol is also an effective lipid depressant in this condition.

The Effect of Venous and Arterial Occlusion on Digital Blood Flow

MILTON MENDLOWITZ and HAROLD ABEL

When blood flow is measured calorimetrically in the great toe or finger tip after release of sympathetic tone by indirect heating supplemented by intravenous tetra ethyl ammonium chloride, arterial occlusion maintained for two minutes or longer will decrease blood flow from 50 to 93 per cent. Venous obstruction on the other hand maintained for the same length of time decreases blood flow from 0 to 39 per cent. Similar differences, although less striking, are obtained with 10 to 30 seconds of arterial and venous obstruction. This indicates that venous obstruction as ordinarily performed may not trap all the inflowing arterial blood, a considerable proportion escaping probably via deep veins, and challenges the validity of venous obstruction plethysmography as a quantitative measure of blood flow.

Observations on the Mode of Thiocyanate Action: Augmentation by Mercurial Diuresis of the Hypotensive Effect of Thiocyanate

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The lowering of basal and casual blood pressure in hypertension by thiocyanate takes several weeks to become manifest, so that its action cannot be due to vasodilation. Attention has been drawn by Healy to the similarity of symptoms of clinical and experimental thiocyanate intoxication to the syndrome of adrenal insufficiency.

Adrenal function was investigated in the present study in hypertensive subjects who had been on thiocyanate therapy for several months (average blood level 8 mgms. per cent), employing the eosinophile count and response of eosinophiles to epinephrine (Laragh modification of Thorn test). Control eosinophile counts were normal, and an average fall in blood eosinophiles of 55 per cent occurred following epinephrine, which was identical with the responses in eight normal subjects. The eosinophile response is an index of 11-oxysteroid activity, but there is no evidence that the adrenal steroids are separately affected by pharmacological agents, so that this test serves as an index of over-all adrenal function.

The Robinson-Power-Kepler test of water and salt excretion provides an index of the activity of the salt retaining adrenal steroids in the absence of nephritis. This test was found to be decidedly abnormal in hypertensive subjects, with normal renal function, while receiving thiocyanate. This finding may be due either to a specific depression of the salt retaining hormones of the adrenal, or more probably, in view of the evidence of normal adrenal activity, to a decreased renal tubular re-absorption of salt with increased salt loss.

In addition to salt loss, urinary calcium and phosphate excretion were found to be increased by thiocyanate and blood calcium was significantly elevated, with a decrease in blood phosphorus. These findings, as well as the increased salt loss, are identical with those observed in parathyroid overactivity. Lassitude, muscular weakness and gastrointestinal symptoms, which are the principal side-reactions accompanying thiocyanate administration, are characteristic of hyperparathyroidism. Osteoporosis has been noted during thiocyanate therapy and attention is drawn to several other points of resemblance between the actions of thiocyanate and the parathyroid hormone. It appears likely that the locus of action of thiocyanate lies in renal tubular regulation of electrolyte excretion, similar to the effects of parathyroid hormone described by Albright, and Harrison and Harrison.

Intravenous dosage of 2 cc. of a mercurial diuretic augmented considerably the fall in blood pressure produced by thiocyanate, for periods up to several days. The hypotensive effect of thiocyanate therapy may be enhanced by the administration of small daily doses of an oral mercurial diuretic, best taken at bedtime since diuresis is increased by recumbency, and by liberal fluid intake since salt clearance in hypertensives is increased by a large urinary volume (Farnsworth). This regimen makes unnecessary the use of extreme dietary salt restriction, as in the rice diet, which is impractical in the clinical management of patients with essential hypertension.

Practical Clinical Application of a New Piezoelectric Material

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BALLISTOCARDIOGRAPHY

The doorway to the general use of the ballistocardiograph has recently been opened by the methods of Dock. This method of analysis of cardiac function and action has until recently been done by machines of too great a size and expense.

A modification of Dock's method is presented utilizing a piezoelectric system. This is a system which when it receives a mechanical strain becomes electrically charged and hence generates an electrical potential. Previously, the elements used were not stable, but with the introduction of barium titanate ceramic elements, there has become available a suitable material for this type of pickup.

The capacity of the element is .065 microfarads and can be increased if necessary. It can withstand temperature of 100 degrees without damage. The element is quite thin and does not affect the characteristics of the reed to which it is attached.

The instrument has the piezoelectric plates mounted on a metal strip which is attached cantilever fashion to a base. With the patient supine, the crossbar is placed across the patient's bare legs and against the bottom of the cantilever, bearing slight pressure against the latter.

The heart's recoil and the blood's impacts cause headward and footward displacement of the legs. When this occurs, the cantilever is bent one way or the other. A voltage is induced with each directional movement and is recorded by a standard electrocardiograph.

The electrical output of this system is of such a magnitude that should one wish to record velocity or acceleration, it is possible to introduce a relatively simple electrical network which would make this conversion.

Oral Treatment of Pernicious Anemia with Vitamin B_{12}

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Five patients with pernicious anemia in relapse were treated with daily oral doses of 75 to 150 micrograms of vitamin B_{12} for periods up to seven months. The reticulocytosis was submaximal but clinical and hematologic response was satisfactory. Improvement in neurologic status occurred in one of the cases showing evidence of combined system disease. One patient failed to respond to an oral daily dose of 150 micrograms and a second to quantities up to 250 micrograms a day. Both persons responded favorably to subsequent parenteral administration of vitamin B_{12}. Two other patients received 2 grams of desicated hog duodenum mucosa and 10 micrograms of vitamin B_{12} daily for 2 months. The reticulocyte response was suboptimal but the rise in hemoglobin and red blood cells was satisfactory. Clinical improvement occurred early in the course of treatment, and has continued. Two additional patients were given oral daily doses of 1.67 milligrams of folic acid and 25 micrograms of vitamin B_{12} for 5 weeks. The reticulocytosis was maximal and the rise in hemoglobin and erythrocytes rapid. Increase of leukocytes above 5,000 per cu. mm. was slow. Clinically the im-

provement was early and progressed favorably. Glossitis in one patient disappeared in a week and neurologic symptoms regressed soon after therapy was begun. A third patient has recently been started on treatment with the same combination of vitamins. He shows a similar clinical and hematologic response and an optimal reticulocytosis.

*A New Coumarin Anticoagulant (Tromexan) 4,4' dihydroxydicumarnyl ethyl acetate: Preliminary Report of Its Action**

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Since July 1949 observations have been made of the effect in animals and humans of a synthetic anticoagulant of the coumarin series, 4,4' dihydroxydicumarnyl ethyl acetate (Tromexan) which is a derivative of 3,3' methylenebis 4 hydroxycoumarin (Dicumarol). Tromexan is a colorless crystal, melting point of 173°C., and four to six times more soluble than Dicumarol.

Originally synthetized by Link, Overman et al. in 1942, Remis and Kubik, in 1945, Pulver and Von Kaulla in 1946, Payling Wright in 1949 have tested it clinically in Europe. The drug has been studied clinically for the first time in the United States in our laboratories. Pharmacological data reveal that the drug, per milligram, has about one sixth the potency of Dicumarol and is about one twentieth as toxic in animals. Ld 50 for single dose in mice is 750 mg/kg, in rats and rabbits 1.5-1.8 grams/kg. One hundred milligram doses in rats fed for 14-20 days failed to produce any toxic symptoms.

Three series of studies are herein reported: the administration of 1) varying single doses to rabbits, 2) single doses to normal humans, 3) therapeutic doses to patients with thromboembolic diseases. Observations were made on the anticoagulant and toxic manifestations of the drug. Complete pharmacological data will be reported elsewhere by Dr. Gruber of Jefferson Medical College.

The anticoagulant effect of the drug was measured by the Link-Shapiro modification of the Quick method. Determinations included the whole plasma and the 12.5 per cent plasma. Results were twice checked by separate technicians.

Animal Experiments: Because of individual and species variations rabbits were first standardized according to the technique of Link, Campbell and Overman. Resistant animals were eliminated. To the sensitive animals pH11 NaOH solutions of Tromexan was tube fed in doses of 100, 200, 300, 400, 500, 600 mgs. Prothrombin times were done at 6 hour intervals around the clock. No changes were noted in the first six hours. Slight elevations were noted in rabbits at the end of 12 hours while at 18 and 24 hours, consistent and reproducable prolongation of the prothrombin times were evident. The normal time (10-12 sec.) was doubled in 18-24 hours with readings of 22-24 seconds at 18 hours and 26-35 at 24 hours, depending upon dosage. Peak prolongations came at 30-40 hours with a return to normal in 12 to 18 hours thereafter.

Studies in Man: Normal control individuals were given single doses of 1200, 1500, 1800 mgs. Twenty four hours after administration of the larger doses the prothrombin times have uniformly reached a level of 25-35 seconds (undilute) and 65-100 (dilute). With doses of 1200 mgs. lower levels were achieved. The minimum time in which consistent changes in the undilute were effected was 15-18 hours. However some cases showed slight elevations (2-4 sec.) in the undilute and 6-12 seconds in the 12.5 per

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cent plasma 12 hours after the initial dose. No evidence of toxicity was evidenced in the normal group. Following a single dose the plasma shows a maximum in hypoprothrombin at 28-36 hours and returns to normal at 60-72 hours.

Fifty patients with thromboembolic disease including coronary occlusion, thrombophlebitis with and without embolic phenomenon have been treated. To date only one case, of severe Laennec's cirrhosis with coronary occlusion showed slight changes in his cephalin flocculation. No other cases showed immediate or delayed toxicity either clinically or as observed by red and white cell counts, sedimentation rates, urine analysis, PSP tests, BSP tests, cephalin flocculating thymol turbidity and total protein determinations.

An initial dose of 1200, 1500 and 1800 mgs. was usually given followed by a maintenance dose of 600-900 mgs. once a day. Some diurnal variation was evident on a single daily dosage, and a few patients required divided doses. With this regimen therapeutic hypoprothrombinemia (27-37) was usually achieved within 18-24 hours after initial dosage. It should be emphasized that no more than 24 hours should lapse between maintenance doses, except where the prothrombin time is excessively prolonged. Clinically the patients showed a satisfactory response to Tromexan as an anticoagulant.

This new coumarin derivative, Tromexan appears to be faster absorbed and excreted than Dicumarol. Further cooperative studies are now in progress.

The Diagnosis of Lymphogranuloma Venereum With Special Reference to the Complement Fixation Test

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Because of the inadequacy of clinical criteria alone in the diagnosis of lymphogranuloma venereum and because of the limitations of the Frei Test in differentiating active from old inactive infections, alternative laboratory methods have been sought.

The author studied a group of 31 patients diagnosed clinically as having inguinal lymphadenitis due to the virus of lymphogranuloma venereum, using the quantitative complement fixation test. In addition, three patients with extra-inguinal involvement were observed. All patients were treated with full doses of sulfadiazine for at least two weeks, and the serologic response to therapy was noted.

The procedure employed was a slight variant of that originally described by McKee, Rake, and Shaffer in 1940. Lygranum C. F., a commercially prepared antigen was utilized.

RESULTS

1. Of 31 cases of inguinal lymphadenitis, 80% had titres of 1:20 or more, on admission to the hospital. By the end of the second week, 94% of this group had titres of this magnitude.

2. Three cases of extra-inguinal disease, one of proctitis, one of a prolonged fever, and one of penile granuloma, all had titres of 1:40 or more.

3. In 22 cases, multiple serum samples were studied. Titre changes were noted in 13. In 5, fourfold or greater rises in titre occurred in the first two weeks. In 8, only titre falls occurred, and in 7 of these, the fall occurred after the second week.

4. In 7 cases, the C.F. test was positive before the Frei test.

CONCLUSIONS

The quantitative complement fixation test is a valid and specific test for lymphogranuloma venereum. It can be quantitated, and the data so obtained are of considerable help in diagnosing the disease. Titres of 1:20 or more are considered significant, as are fourfold changes in titre, whether they are rises or falls. Repeat determinations with observations for changes in titre will help differentiate recent from old infection. It is the best single laboratory test, clinically available at present, to confirm or eliminate the diagnosis of lymphogranuloma venereum.

The Lupus Erythematosus ("L.E.") Cell

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The L.E. cell is the product of the interaction of the cellular elements of the peripheral blood or bone marrow and of a plasma factor, the latter unique for patients having acute disseminated lupus erythematosus.

The plasma factor has been demonstrated by us to be a gamma globulin, using the protein fractionation method of Svennson. This gamma globulin is frequently active in high dilution and can be titered. It is stable under temperatures varying from 0 degrees centigrade to 56 degrees centigrade. Complement is not required for its action. Spontaneous or induced remission may diminish its activity but in our series has not caused a complete disappearance of activity.

Serial studies indicate that the L.E. cell may begin as a peculiar autolytic process in one or all lobes of a polymorphonuclear leukocyte nucleus. In the former instances the whole development occurs within the given cell. The affected lobes undergo change, the altered cell becomes the center of a clump of apparently unaltered polymorphonuclear leukocytes, one or two of which ingest the material.

Previously published articles have emphasized the necessity of the presence of an anticoagulant for the formation of L.E. cells. We have been able to demonstrate L.E. cells taken directly from clotted blood of L.E. patients. The implications of this finding have not yet been explored.

Histochemical studies have been undertaken to define the nature of the ingested or altered material. By use of specific stains and absorption of appropriate monochromatic light, we have been able to show that the material is nuclear desoxyribosenucleic acid, partially intact and partially depolymerised, i.e., there is a differential absorption using Feulgen and methyl green stains. These findings relate the L.E. cell to the hematoxylin body.

Studies on Uterine Sinus and Amniotic Fluid Pressures in the Full-term Pregnant Uterus

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It seemed to us that a knowledge of the pressures in the uterine venous system would not only be of academic interest, but would most likely prove of practical value. With this in mind, we undertook a study of the pressures within the uterine sinuses, the intact amniotic sac, and pressure changes occasioned by intrauterine packing.

MATERIALS AND METHODS

Patients were selected in whom elective cesarean section was to be performed. With the uterus exposed, a transfusion needle of the Unger or Kaliski type was inserted into a uterine sinus. In almost any area punctured, a venous flow was readily obtained. When blood was seen to flow freely, a standard spinal manometer was attached to the needle by means of a five inch length of rubber tubing, the manometer and tubing having been previously filled with 2.5 per cent sodium citrate solution. The reading was taken directly from the manometer. For the amniotic sac readings, the manometer was attached after amniotic fluid began to flow from the needle.

Pressure changes created by gauze packing were measured by means of a water filled balloon inserted into the uterine cavity and attached to the manometer system.

In ten cases, a comparison was made between the prothrombin time, sugar and urea in the uterine and general circulation, blood being drawn simultaneously from the uterine sinus and the antecubital vein. These determinations were discontinued after noting that there were no significant differences.

Uterine sinus pressures were determined in thirty-four patients. The lowest reading was 60 mm. of water and the highest 300 mm. of water, giving an average of 180 mm. of water.

The pressure in over 60 per cent of the cases was between 150 and 230 mm. of water.

The pressure of fluid in the amniotic sac was determined in six patients. In one case, the pressure was found to be 60 mm. of water and the other five ranged between 150 and 340 mm. of water.

In a patient in whom the uterine sinus pressure was found to be 60 mm. of water, the pressure rose to 120 mm. after the cavity was packed with five yards of gauze; to 170 mm. when the cavity contained ten yards; and to 295 mm. when the total gauze content of uterine cavity was fifteen yards.

We believe that the above findings may prove significant in the treatment of postpartum uterine hemorrhage. We are led to this belief by the physical fact that liquids cannot escape when a greater force is opposed to the open segment of a fluid system. An intrauterine pressure greater than the one in the vessel from which leakage is taking place should cause arrest of bleeding. Higher pressures can be readily obtained by means of gauze packing or an intrauterine balloon containing a sterile liquid.

*Treatment of Pulmonary Emphysema with Pneumoperitoneum**

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Twenty-two patients with far advanced pulmonary emphysema and incapacitating dyspnea were treated with pneumoperitoneum. Three of these also had pulmonary tuberculosis and three were thoracic surgical patients whose postoperative course was complicated by severe emphysema and related inability to raise secretions.

Investigation before treatment consisted of extensive clinical evaluation of their cardio-pulmonary status and studies of pulmonary function, including determination of maximum breathing capacity, vital capacity and its subdivisions, and residual air.

Clinical observations after treatment revealed improvement in seventeen patients. This was characterized by lessened dyspnea, reduction of sputum, and increased exercise tolerance. All patients, including those not otherwise improved, noted increased tussive force and greater facility in raising tracheobronchial secretions.

The most characteristic physiologic changes after treatment were a marked reduction of the residual air, a notable increase of the complementary air and a small reduction of the total lung volume. The maximum breathing capacity was increased in all patients and the vital capacity was increased in some.

Pneumoperitoneum treatment was most effective in patients with diffuse "obstructive" emphysema. It was of least value in patients with marked pulmonary fibrosis and in those with single or multiple large blebs.

Other methods of treatment of pulmonary emphysema were reviewed, the technique of pneumoperitoneum administration was described, typical roentgen ray plates of the chest were illustrated and indications and contra-indications for this type of treatment were outlined.

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*Vagotomy Versus Gastric Resection: A Critical Evaluation of Two Methods of Surgical Treatment of Duodenal Ulcer**

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The present report attempts to evaluate critically the relative effectiveness of vagotomy alone and subtotal gastric resection alone as definitive elective surgical procedures for the patient with intractable duodenal ulcer. The material is derived from 263 consecutive subtotal gastrectomies performed at the U. S. Veterans Hospital, Bronx, New York, during the three-year period from January 1, 1945 to December 31, 1947. For comparion is a series of 54 consecutive vagotomies performed from August 30, 1946 through September 15, 1948, representing every vagus nerve section ever performed at this hospital. The following breakdown demonstrates the indication for operation in each of the sub-groups:

	Gastrectomy	*Vagotomy*
Duodenal Ulcer without obstruction	95	43
Duodenal Ulcer with obstruction	71	0
Gastric Ulcer	37	0
Marginal Ulcer	11	11
Emergency Bleeding Ulcer	2	0
Total All Ulcers	216	54
Malignancy	47	0
Total	263	54

In this analysis we are specifically concerned with the top listed group of 138 cases in which the indication for surgery was an intractable non-obstructing duodenal ulcer with or without bleeding. In this group 95 cases were treated by subtotal gastrectomy with three deaths, a case fatality rate of 3.2 per cent,—and forty-three cases by vagotomy with one death,—a case fatality rate of 2.3 per cent. Both groups are comparable not only as to the indication for surgery but also with regard to race, sex, age, general physical condition, and the surgeons performing the operations.

Excluding two cases of vagotomy which were combined with another operative procedure, follow-up was secured on 94.7 per cent of the cases treated by gastric resection and 100 per cent of the cases treated by vagotomy. Average follow-up period for the two groups was two and one half years.

In these two selected groups, the end results were as follows:

	End Results	*Gastrectomy*	*Vagotomy*
Excellent	—Symptom Free...	39 43%	8 19%
Good	—Mild Symptoms..	32 36%	14 34%
Fair	—Symptoms present but improved over preoperative status.....	8 9%	6 15%
	Total-Improved ..	79 88%	28 68%
Failure	—Complication requiring further surgery or recurrence of preoperative symptoms	8 9%	12 30%
Death	—Postoperative ...	3 3%	1 2%
	Total-Failure ...	11 12%	13 32%

It would appear from this analysis that despite its lower mortality rate, vagotomy is considerably inferior to gastric resection as a definitive procedure for the treatment of intractable duodenal ulcer.

* From the Surgical Service of U. S. Veterans Hospital, Bronx, N. Y. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Irradiation of Advanced and Radio-resistant Cancer through a Grid

HIRSCH MARKS

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1. Irradiation through a grid has extended the range of x-ray therapeusis to tumors hitherto adjudged irresponsive to x-rays, namely:

a. Metastatic carcinoma of regional lymph nodes
b. Extra-vesicular extension of carcinoma of the urinary bladder
c. Recurrent inoperable pelvic carcinoma
d. Advanced intraoral carcinoma
e. Radio-resistant Hodgkin's disease.

To bring this to fruition, we substituted irradiation through multiple small fields for irradiation through large fields. The sizes of these fields are:—0.5 x 0.5 cm., 1 x 1 cm., and 2 x 2 cm. in a 10 x 15 cm. or 6 x 8 cm. lead-rubber shield, 3 mm. thick. The open portals alternate as in a checkerboard with as many covered areas. This effects a near-total elimination of back-scatter. The excessive absorption of the latter in the intervening normal tissue, is the real hindrance to the attainment of an adequate depth dose, as the full impact of the effective wave-length is brought to bear on the skin and subcutaneous tissues overlying the tumor. The narrowing of the irradiated volume results in an initial drop in intensity of the beam which is compensated by a 3, 6 or 12 fold increase in exposure.

2. Despite the enormous doses mentioned above, the hazards to the skin and normal tissues overlying the tumor of the patient are reduced to a minimum and the general systemic reactions are relatively non-existent. Desquamation and denudation of the skin follows after completion of 24,000r in air, and is the result of the back-scatter diffused from the depth of the tumor upwards. This is in contrast to irradiation through large fields where the same skin reactions result after a much smaller total dose, and the patient is subject to severe radiation sickness.

3. The over-all treatment time is greatly reduced by the delivery of higher daily doses, to wit, 600, 1200 and 2400r in air.

On the Deposition of Stilbamidine and 2-Hydroxystilbamidine in Cytoplasm and Nuclei of Different Organs and Tumors

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Administration of stilbamidine and 2-hydroxystilbamidine to patients with myeloma results in the formation of granules in the cytoplasm of the myeloma cells.[1, 2] These granules can be stained with Wright stain and have been proven to consist of ribose nucleic acid linked either with stilbamidine or 2-hydroxystilbamidine.[3] Quantitative methods for the determination of these diamidines in organs have been developed,[4] which made possible the study of the distribution of these substances in various organs of the body.

We were able to confirm the results of Hawking and Smiles,[5] who with qualitative methods found stilbamidine and 2-hydroxystilbamidine in liver and kidneys whereas in spleen and lungs only traces of the diamidines can be discovered. Because of the marked affinity of these diamidines to the liver parenchyma, the deposition of these compounds in a transplantable mouse hepatoma was investigated. It appears that after subcutaneous injection, considerable amounts of the diamidines can be found in the hepatoma. Therefore, the diamidines are de-

posited not only in the normal liver but also in a malignant tumor derived from liver cells. Other tumors behave differently. If mice bearing a transplantable lymphosarcoma, or a transplantable mammary cancer, are injected with these diamidines, the tumors contain only traces of these compounds.

Examination of imprints of organs of animals treated with these diamidines has elicited a remarkable difference between these two compounds. When these imprints are studied with a fluorescence microscope only small amounts of fluorescent material can be visualized in the animals treated with stilbamidine. Traces of fluorescing substance can be found in the cytoplasm only and sometimes between the cells. On the other hand, examination with the fluorescence microscope reveals large amounts of 2-hydroxystilbamidine in the organs of animals treated with this compound. This fluorescent material is partly present in the cytoplasm and between cells, but mainly in the nuclei. After injections with 2-hydroxystilbamidine the nuclei of liver cells, kidney cells and of the cells of the transplantable hepatoma become strongly fluorescent. After injection of 2-hydroxystilbamidine only small amounts of the fluorescent material are seen either in cells or in nuclei of lungs and spleen. The same negative result is obtained when imprints of the transplantable lymphosarcoma and mammary carcinoma are studied: after treatment with 2-hydroxystilbamidine no fluorescent material can be visualized in these tumors.

It can be surmised that the same distribution of the compound takes place in the organs of humans who are treated with 2-hydroxystilbamidine. We have observed that the nuclei of liver cells of such patients become highly fluorescent too. Nevertheless, we have seen that in humans, after treatment with 2-hydroxystilbamidine, the renal function as tested with phenolsulphonphthalein, and the liver function as tested with bromsulphalein test remained normal.

These diamidines are excreted in urine[6] and bile.[7] It could, therefore, be assumed that these substances are only accumulated in the cells of excretory organs. This might also be the reason for the accumulation of this substance in a hepatoma, a tumor derived from excretory cells. This assumption, however, is incorrect because large amounts of 2-hydroxystilbamidine can be visualized in the brain. In the brain of cancer mice treated with this substance large numbers of ganglion cells exhibit fluorescent nuclei. Unfortunately, the quantitative determination of 2-hydroxystilbamidine in brain substance, presents for the time being, great analytical difficulties. The accumulation of this diamidine in the brain may perhaps explain the trigeminal neuropathy which is a constant side action of another diamidine, that is, of stilbamidine.[8]

The difference between stilbamidine and 2-hydroxystilbamidine should be stressed. As far as can be seen stilbamidine links up only with the ribosenucleic acid of the cytoplasm and does not penetrate into the nuclei of the cells. The introduction of a hydroxy-group evidently increases the powers of penetration of the diamidine. Thus, 2-hydroxystilbamidine not only penetrates through the nuclear membrane and connects with the desoxyribose nucleic acid of the nuclei of liver and kidney cells, but it also reaches the brain which, as a rule, is well protected against the introduction of chemical substances.

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Electrokymographic Studies of the Relationship Between the Electrical and Mechanical Events of the Cardiac Cycle

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Studies of possible correlation between the electrical and mechanical events of the cardiac cycle have long been of interest. The initial modern studies were done by Wiggers[1] in 1923, and Lewis[2] in 1925 though earlier work had already been recorded.[3-5] Katz[6] made animal studies in which right and left ventricular pressures as well as pulmonary artery and aortic pressures were recorded by an optical manometer. Clinical studies correlating the electrocardiogram and carotid artery pulsations were done by Wolferth and Margolies.[7,8] These latter investigators assumed that left bundle branch block, as recorded on the electrocardiogram, would cause the left ventricle to contract later and therefore cause a later arrival of the pulse wave in the carotid artery than is normally the case. Nichol[9] made a similar study in 1933. Katz[10] criticized the work of Wolferth and Margolies. He employed the same technique but failed to note a correlation between the mechanical and electrical events of the cardiac cycle. Castex, Battro, and Gonzalez[11] attempted to correlate the site of origin of ventricular premature contractions with the interval from the onset of the QRS complex to the onset of the pulse wave in the carotid artery. Kossmann[12] in 1947 studied mechanical and electrical events of the cardiac cycle in the W.P.W. Syndrome.

The development of the electrokymogram allowed us to undertake such a study by a new technique. Ellinger and his co-workers[16] published a study of ventricular asynchronism as recorded by electrokymograms of the pulmonary artery and ascending aorta in 16 cases of bundle branch block, using the carotid artery pulsation as a reference point for comparison of the electrokymograms.

We have studied 25 cases of bundle branch block. By means of a new three-channel direct-writing recording apparatus and two electrokymograms, we have been able to record the electrokymogram of the pulmonary artery and ascending aorta simultaneously in the right anterior oblique position, thus eliminating use of the carotid artery pulsation as a reference point (as Ellinger and his co-workers[16] did) and thereby greatly increasing the accuracy of our measurements. In over 50 normals, electrokymograms of the two great vessels were made by this and other techniques and we found that the range of normal was from plus .03 to minus .02. That is, the upstroke of the pulmonary artery at the onset of its expansion was .03 seconds ahead of the upstroke of the ascending aorta at the onset of its expansion. In other cases the upstroke of the pulmonary artery was .02 seconds or .01 seconds ahead of the upstroke of the ascending aorta. In some the difference was .00, that is the upstrokes were equal in time. In others the upstroke of the ascending aorta was .01 seconds or .02 seconds ahead of the upstroke of the pulmonary artery, and these intervals we considered as negative, that is minus .02 and minus .01.

In the 25 cases of bundle branch block, we found that in only 8 cases was it possible to correlate the mechanical and electrical events of the cardiac cycles. In 17 of the cases, the relation between the onset of the pulmonary artery and the onset of the ascending aorta was within the normal range of limits. In all cases the diagnosis of bundle branch block was made from the standard and precordial leads, using the intrinsicoid deflection of the precordial leads to decide the side of the bundle branch block.

It is thus apparent that a correlation between electrical and mechanical events of the cardiac cycle is not possible, at least by this technique. It should be noted that in a case of right bundle branch block with a QRS of .12, that the pulmonary artery was .05 seconds ahead of the ascending aorta,

Results		Relation of Pulmonary Aorta and Ascending Aorta*	Correlation of Electrical and Mechanical Events
A. Cases of Incomplete RBBB. QRS Duration (QRS .11 or .12)			
	1. .12	+.02	No
	2. .11	+.04	No
	3. .11	—.06	Yes
	4. .11	+.03	No
	5. .12	+.05	No
	6. .12	—.02	No
B. Cases of Complete RBBB. QRS Duration (QRS greater than .12)			
	1. .13	—.04	Yes
	2. .14	—.09	Yes
	3. .14	.00	No
	4. .14	.00	No
	5. .13	+.04	No
	6. .13	.00	No
	7. .15	.00	No
C. Cases of Incomplete LBBB. QRS Duration (QRS .11 or .12)			
	1. .12	+.08	Yes
	2. .12	+.03	No
	3. .11	+.05	Yes
	4. .12	+.02	No
D. Cases of Complete LBBB. QRS Duration (QRS greater than .12)			
	1. .15	+.08	Yes
	2. .14	+.01	No
	3. .13	—.03	No
	4. .15	+.02	No
	5. .14	+.01	No
	6. .13	+.06	Yes
	7. .14	+.05	Yes
	8. .14	+.02	No

* A plus sign means that the onset of pulmonary artery upstroke precedes that of the ascending aorta. A minus sign means the reverse.

well outside the normal range, but in a direction opposite to that expected if there were correlation between the electrical and mechanical events. In a case of complete left bundle branch block with a QRS of .13 seconds, the ascending aorta was .03 seconds ahead of the pulmonary artery, again a relation outside the range of normal but in a direct opposite to that expected.

Finally, it should be noted that repetition of the curves at different times leads to the same results—the results are reproducible.

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Ventricular Contraction in Wolff-Parkinson-White Syndrome: An Electrokymographic Study

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Ample evidence exists that in the Wolff-Parkinson-White syndrome there is premature activation of the ventricles (ventricular pre-excitation), usually of the right ventricle but occasionally of the left. There has been a great deal of disagreement, however, concerning the mechanical behavior of the ventricles, i.e., whether asynchronism of ventricular contraction results from pre-excitation.

The methods employed in the past for the detection of the presence or absence of ventricular asynchronism were based on the simultaneous recording of the venous and arterial pulse tracings, phonocardiogram, and electrocardiogram. By these tracings asynchronism was uniformly demonstrated in bundle branch block but uniform results were not obtained in Wolff-Parkinson-White syndrome. A more precise comparison of right and left ventricular ejection has recently been obtained by simultaneous recording of peripheral arterial pressure and right ventricular pressure during cardiac catheterization. No asynchronism was observed by this method in one case of Wolff-Parkinson-White syndrome.

The introduction of electrokymography has made available a simple and accurate method of determining ventricular asynchronism from the onset of the aortic and pulmonary kymographic curves which indicate left and right ventricular ejection, respectively. Normally there may be a physiological lag of ± 0.03 sec. between aortic and pulmonary artery ejection. This method has uniformly demonstrated the presence of mechanical asynchronism of the ventricles in bundle branch block, with a lag of 0.04 to 0.07 sec. between aortic and pulmonary artery ejection, depending on the bundle branch affected. It would be expected that if ventricular asynchronism were present in Wolff-Parkinson-White syndrome a similar lag between aortic and pulmonary ejection would be observed.

In an attempt to throw light on this disputed subject we have carried out detailed electrokymographic studies in 4 cases of Wolff-Parkinson-White syndrome with typical electrocardiographic features. By means of a 4-channel apparatus the electrokymogram was recorded simultaneously with the electrocardiogram, carotid pulse curve and phonocardiogram. The time of onset of the isometric and ejection phases of systole in the kymographic curves from the aorta, pulmonary artery, left ventricle and right ventricle in relation to the other reference tracings was measured.

In one case the aortic and pulmonary artery kymograms were simultaneous and in the other three cases pulmonary artery ejection preceded that of the aorta by 0.02 sec. The latter lag is within the normal physiological range. Analysis of the left and right ventricular kymograms yielded similar measurements. These observations indicate a lack of asynchronism in left and right ventricular ejection.

Our finding of absence of significant asynchronism of the ventricles in the presence of ventricular pre-excitation correlates well with the observations of the intracardiac and esophageal electrocardiograms in our cases recorded by Grishman, Steinberg and Kroop. These records indicate that there was pre-excitation not only of the right ventricle but also of the left in all four cases. This suggests that both ventricles are stimulated prematurely by aberrant impulses through accessory A-V pathways rather than through the His and Purkinje conduction system. The pre-excitation of both ventricles explains the lack of asynchronism in contraction in our cases.

Blood Volume and Electrolytes in Induced Acute Hypoglycemia in Diabetics

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Twenty-one patients, of whom 19 were diabetic and 2 non-diabetic, were rendered acutely hypoglycemic by intravenous injections of insulin. Before administration of insulin, control observations were made of blood volume and electrolytes and the urine was studied. After injection of insulin, frequent samples of urine and blood were examined until sugar fell to 40-50 mg. per cent and/or severe hypoglycemic symptoms appeared. Blood volume was determined by the dye method, initially with multiple doses of Congo-Red and later with Evans-Blue (T 1824). The findings were as follows:

A. Blood Electrolytes:
1. Ca invariably rose.
2. Inorganic P invariably fell.
3. Na rose in all but one case and in that patient there was no significant change.
4. K rose in all but one individual but there was no significant change in that patient.

B. Blood Volume:
1. Invariably reduced
2. The Hematocrit remained at the original level or was reduced.

C. Urine:
1. P excretion increased.

D. The non-diabetics showed the same serial changes as the diabetics.

In induced hypoglycemia in diabetics and non-diabetics, the inorganic P of the blood fell while the excretion of P in the urine rose. Despite the inadequacies of the dye method for blood volume determination, the consistency of our findings indicates a reduction in circulating blood volume. Unexpectedly, most of our cases showed a decreased and none an increased hematocrit, indicating that proportionately more red cells are removed from the circulating blood than plasma. The only parallel to such a fall in blood volume with decreased hematocrit, with which we are acquainted, is that in rabbits when shock is produced by suspending them by the hind legs.

CONCLUSIONS

Hypoglycemia produces a fall in blood volume of an unusual type in that the hematocrit falls as a result of a proportionately greater loss of red cells than plasma. The fall in hematocrit is unexplained. The reduction in circulating blood volume explains the rise of Ca, Na and K. The inorganic P of the blood falls while, pari passu, the excretion of P in the urine increases. Diabetics and non-diabetics react similarly to induced hypoglycemia.

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The Heritage in Otosclerotic Deafness

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Biochemical blood pathologies are presented pertaining to clinical-pathological manifestations in 55 cases of deafened children, of whom 27 were deafmutes; the major number under 10 years of age.

Since 1860[1] geneological charts disclose the heritage of deafness, as an etiological factor in otosclerosis. What the heritage is,

and how it comes into being in succeeding generations have not heretofore been postulated.

Otosclerosis is generally *symptomatic,* presenting progressive deafness as its symptom. Autopsies show another form,—asymptomatic otosclerosis[2] which leaves its victims free of any consciousness of hearing loss.

Reporting 581 cases of deafness with 461 blood biochemical examinations,[3] *the factors at fault* which evolved otosclerotic lesions on the otic capsule and impaired sound perception, are *hyperpyruvenia* and *hypercholesterolemia.*

The children reported herein exhibited *hyperpyruvemia* without exception, thus disclosing a defective mechanism in carbohydrate metabolism *in the enzyme carboxylase.* This deficiency leaves cholinesterase out of control, and this destroys acetylcholine, the mediator of nervous action, along the synapses of the acoustic nerve. Cochlear and vestibular dysfunction results, exhibiting nerve-perception loss which is found on clinical examination.

The secondary phase in cellular pathology occurs because of the evidence furnished by hypercholesterolemia. The lack of lipotropic factors are the background; the deposits of lipids in the arterioles and capillaries of the end-organ apparatus happen because (1) there is deterioration in the health of the endothelial linings, and (2) anoxia of the parts, due to lipid deposits in the vascular supply to the cochlea. Atrophic areas form as a sequence to the deficiency outlined above; the intermediate carbohydrate metabolism of calcium is disarranged, and with phosphorus-calcium ratio imbalance, there occurs abnormal osteoblastic and osteoclastic activity with areas of bone rarefaction and new bone deposits abnormally placed in the layer of the otic capsule. Herein is found the explanatory data making comprehensible the meaning of the otoscopic and functional examinations. This relationship has not heretofore been realized.

From these blood studies, an estimate of the extent of cellular pathology can be made because in the writer's concept, enzymatic biochemical dysfunctions *precede the development of cellular pathology,* and once such dysfunctions are recognized, further evolution of the cellular pathology can at least be stopped by attempting a reversal of the chemical processes.

In many of the adult cases which constituted an earlier series of 581 cases, this has been achieved, with practical, useful gains in hearing acuity in a large number. In the present series of children, the progress is slower, because many of them never comprehended sound symbols, the meaning of which they must first be taught.

The acoustic nerve particularly, and to a lesser extent its vestibular branch, possesses an extremely low resistance power[4] as compared to other cranial nerves, as for example, the facial nerve. The acoustic nerve-end is the youngest in phylogenetic age. It easily succumbs therefore to deleterious environmental elements.

From the foregoing, it would seem desirable that young couples comtemplating pregnancy who have a positive family history of deafness should undertake blood examinations and therapy to attempt reversal of biochemical blood pathology that may be uncovered to the end that the geneologic heritage may be removed before pregnancy is started.

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Dihydroergocornine in the Differential Diagnosis of Functional Heart Disturbances and Organic Heart Disease

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The positive results after the "2-step" exercise electrocardiogram in patients with functional heart disturbance, that is, RS-T depressions and T wave inversions, may be indistinguishable from those observed in the presence of organic heart disease.

Ergotamine tartrate, previously used for making the distinction between organic and functional heart disturbance, was abandoned because of its anginal provoking properties. We have continued our study of this problem utilizing dihydroergocornine (DHO-180), a newer dihydrogenated ergot alkaloid derived from ergotoxine. The safety of this drug for clinical investigation in patients with organic heart disease was confirmed.

We first investigated the effect of intravenous administration of dihydroergocornine on blood pressure, heart rate and the resting electrocardiogram, including its influence on the "2-step" exercise electrocardiogram. Normal controls as well as cases of functional cardiac disturbance and organic heart disease were included in the series. Single injections of DHO-180 were given to 116 patients with repeated dosage on a subsequent day to seven of the subjects. The dosage of DHO-180 was 0.5 mgm. for 116 of the injections; for the remaining seven it varied between 0.25 and 1.0 mgm. The changes observed were found to occur within a few minutes following the intravenous injection, and lasted over one hour. In normotensive subjects the systolic blood pressure showed no significant alteration in half of the cases, and a slight to moderate drop in about two-fifths; the diastolic levels showed practically no significant change. On the other hand, in the hypertensives the systolic levels were decreased in three-fourths of the cases; changes in diastolic levels occurred in slightly less than half. The cardiac rate decreased in nearly all; in these instances the average maximum decrease in rate was -12.7 beats a minute. The resting electrocardiogram was entirely unaltered in one-half the cases; in almost all of the remaining half, there were noted only insignificant electrocardiographic changes (heightening of the T waves and, more rarely, slight RS-T elevations).

The precise explanation for the RS-T segment and T wave alterations in the functional cases remains unresolved as does the exact site of action of the dihydroergocornine. Both problems concern the intricate interrelationship between the autonomic nervous system and the cardio-vascular system, particularly the coronary circulation.

The side reactions to intravenous injection of dihydroergocornine were stuffy nose, nausea, and less frequently, dizziness and postural hypotension, all of which were transient.

The "2-step" exercise tolerance test was performed in a selected group of twenty patients both before and after the intravenous administration of 0.4-0.5 mgm. of dihydroergocornine. In ten of these who were classified clinically as having definite functional heart disturbance, the "2-step" test was positive before DHO-180 but negative after its administration. In the ten patients with unequivocal evidence of coronary artery disease the "2-step" test was positive before and after DHO-180 injection.

Because angina pectoris was not provoked in the organic patients and since there was constant prevention of electrocardiographic abnormalities after exercise by dihydroergocornine in the functional cases, this drug appears to be a safe and promising agent for further investigation in distinguishing functional from organic heart disease.

The Distribution of the Protein-bound Iodine in the Electrophoretic Fractions of Human Serum Studied with Radioactive Iodine

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Although it is generally accepted that the active hormone within the thyroid gland is contained in a specific globulin called thyroglobulin, no such unanimity prevails regarding the nature of the hormone as it actually circulates in the animal organism. The precipitin studies by Hektoen, Carlson and Schulhof and later by Lerman have not been a complete answer to this problem.

Earlier studies from this laboratory, using the relatively crude method of ammonium sulphate and sodium sulphate precipitation, showed that the proteins in the albumin and globulin fractions of the serum were both iodinated. Protein-bound iodine was determined by classical chemical methods.

We have now extended these studies using radio-active iodine. The blood serum of patients, several days after the therapeutic use of I-131, was dialyzed to free the serum of inorganic I-131. The sera were fractionated in an electrophoresis apparatus, the patterns photographed and the various fractions were then tested for their radioactivity which could only be due to the presence of I-131 incorporated in the thyroid hormone secreted after the administration of the radioactive iodine and circulating as protein-bound, presumably hormone, iodine. The specific activity of each protein fraction was then determined on the basis of the total radioactivity and the protein content of the respective samples.

Examination of Table I shows that the tagged circulating thyroid hormone is not uniformly dispersed through the plasma spectrum but that the various protein fractions are iodinated to varying degrees. The gamma globulin is practically free of organically-bound iodine while certain of the other globulin fractions are highly iodinated. We think that this is the first demonstration of the pattern of distribution of the protein-bound iodine in the serum of human subjects. We plan to supplement these studies with a determination of the stable iodine content of the various plasma fractions as isolated by Cohn. We wish to express our sincere thanks to Doctor Kurt G. Stern and Doctor Sergei Feitelberg for their very valuable cooperation in this study.

TABLE I—PROTOCOL OF STUDIES OF ONE SERUM

Electrophoretic Fraction	*Proteins Contained in Fraction*	*Per cent Protein*	*Corrected net counts per second per c.c. serum*	*Specific* Activity*	*Per cent total activity per mg. protein*
Left Upper	albumin alpha globulin	1.49	30.4	20.4	3.3
Left Middle	albumin, alpha, beta globulin	2.43	372.0	153.0	25.0
Left Lower	albumin, globulin	3.30	437.0	132.0	21.6
Right Lower	albumin, globulin	1.52	338.0	222.0	36.4
Right Middle	beta, gamma globulin	1.08	86.9	80.4	13.4
Right Upper	gamma globulin	0.19	0.5	2.6	0.4
Control Serum (dialyzed)	whole serum	4.12	506.0	123.0	

* Counts per second divided by per cent protein in sample
All counts in Q-gas counter

The Renal Clearance of Aureomycin in Man

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Simultaneous renal clearances of aureomycin and endogenous "creatinine" were performed in ten subjects and of aureomycin, inulin and endogenous "creatinine" in five subjects convalescing from various infectious diseases requiring the oral administration of this antibiotic. Two hundred and fifty mgm. of the drug were ingested every four to six hours, the last dose being administered two hours before the onset of the clearance studies. The plasma levels of aureomycin ranged between 0.5 and 6.0 gamma/cc. with one extreme of 14 gamma/cc. in a subject with moderate renal insufficiency. In any one individual the plasma concentration varied little throughout the period of observation. In an additional five subjects aureomycin glycinate was administered as an intravenous drip and the renal clearances studied during rising and falling plasma concentrations of aureomycin through the range of 2.5 to 15 gamma/cc. Inulin was given as an intravenous infusion at rates calculated to maintain plasma concentrations of 30 mgm./100 cc. The renal clearances of inulin and endogenous "Creatinine" were used as measures of glomerular filtration rates.

Aureomycin concentrations in plasma and urine were determined by the fluoro-photometric method of Saltzman,[1] which has a maximum analytical error of 10 per cent and checks well with the biological method of Dornbush and Pelcak.[2] Inulin was determined by Schreiner's[3] modification of the resorcinol method and endogenous "creatinine" by the Bonsnes and Taussky[4] modification of the Jaffe reaction.

With the orally administered drug the aureomycin clearances averaged 44.5 per cent of the inulin clearances, with a range of 39.7 to 50.9 per cent, and 45.6 per cent of the endogenous "creatinine" clearances, with a range of 38.2 to 50.0 per cent. With the intravenously administered drug the aureomycin clearances averaged 38.8 per cent of the inulin clearances. In two of these latter subjects there was a moderate depression of the aureomycin/inulin clearance ratios at the higher aureomycin plasma concentrations. In the other three subjects the clearance ratios remained relatively constant throughout all ranges of plasma aureomycin concentrations studied. There appeared to be no correlation between urine flow and the clearance ratios in all of the fore-going studies. Preliminary studies suggest that the slightly higher clearance values obtained when the drug is administered orally, as compared to the intravenous route, may be due to the longer exposure to metabolic processes through the former route, with the production of degradation products of aureomycin which fluoresce but which may be biologically inactive and excreted in a different manner than the parent drug.

In 4 of the subjects receiving aureomycin by mouth mannitol osmotic diuresis was induced following three control periods. In all of these subjects no change was induced in the aureomycin/inulin clearance ratios, suggesting that tubular reabsorption of aureomycin does not play a significant role.

Ultrafiltrates were obtained from 6 plasma specimens drawn from two of the subjects receiving intravenous aureomycin. Analyses of these ultrafiltrates revealed that between 65 to 70 per cent of the drug was bound to unfilterable plasma components. The renal clearances of filterable aureomycin approximated the simultaneous inulin clearances closely, the average free aureomycin/inulin clearance ratios being 0.94 and 0.98.

It is concluded that the renal excretion of aureomycin occurs through glomerular filtration of the filterable fraction of the drug alone. It is cleared at approximately 45 per cent of the glomerular filtration rate when given orally, and at about 35 per cent of the glomerular filtration rate during intravenous administration. The rate of clearance of the drug is influenced solely by the glomerular filtration rate and the plasma

protein binding. Tubular mechanisms do not play a significant role. The excretion rate is not influenced by osmotic or water diuresis. For practical purposes therefore the urinary concentration of aureomycin in any one individual is directly proportional to the plasma concentration and inversely proportional to the urine flow.

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The Effect of Aureomycin Therapy in Infectious Mononucleosis (A Further Preliminary Study)

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From preliminary studies and this further preliminary work, Aureomycin appears to be of definite benefit in the therapy of infectious mononucleosis. The protean nature of the manifestions of this disease make concrete evaluation of any new form of therapy difficult. Subjective and objective findings in control and aureomycin-treated groups are compared in this report.

We are reporting eighteen cases treated with Aureomycin and twenty-five control cases on symptomatic therapy and bedrest alone. Aureomycin was given in doses of 0.5 grams, four times daily for six days, in all but one patient who received only 0.25 grams, four times daily. For the large part of the series, control was established by alternating cases for control and special study series.

For lack of any one specific criterion to evaluate the progress of this disease, we have compared these manifestations:

a. Duration of hospitalization and duration of the course of the clinical disease.

b. Duration of fever.

c. Changes in total and differential leukocyte count.

d. Heterophile agglutination.

e. Splenomegaly.

f. Incidence and duration of hepatic involvement.

g. Effect of symptoms.

DURATION OF HOSPITALIZATION AND OF CLINICAL COURSE OF DISEASE.

The maximum, minimum and average for each of these groups is given in the following table:

Days of Hospitalization	*Maximum*	*Minimum*	*Average*
Without Aureomycin	161	10	39
With Aureomycin	67	10	26

Days of Disease	*Maximum*	*Minimum*	*Average*
Without Aureomycin	164	15	44
With Aureomycin	67	14	32

The significance of the difference in the average figures may be borne out by the fact that in the Aureomycin-treated group the disease was terminated in less than thirty days in 72 per cent of the cases as compared to 36 per cent in the patients receiving only symptomatic therapy. Duration of the hospital stay was comparable

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in the two groups to the duration of the disease.

Duration of Fever: The duration of fever has shown striking alteration with use of Aureomycin therapy. With Aureomycin therapy 40 per cent of the patients returned to normal temperatures in twenty-four hours after treatment was started and 70 per cent within seventy-two hours. In the control group the shortest febrile reaction was four days and only 56 per cent were afebrile within fourteen days from the onset of the disease.

Total and Differential Leukocyte Count: There was no remarkable decrease in duration of abnormal leukocyte and differential counts in the Aureomycin treated group. In fact, in a few isolated cases the number of atypical mononuclear cells seemed to increase after the start of Aureomycin therapy. In both groups, the abnormal differential count and atypical lymphocytic cells lasted well into the convalescent stage of the disease.

Heterophile Agglutination: The heterophile agglutination titres were extremely variable in both groups. Of those cases receiving symptomatic therapy alone, 16 per cent developed no significant heterophile titre (1:128 or over).

This is consistent with other reports on the incidence of titre of heterophile agglutinins. Of those treated with Aureomycin, 44 per cent developed no significant titre, and in those who received Aureomycin within ten days of onset of the disease, 60 per cent did not develop a significant positive titre.

Splenomegaly: Splenomegaly was recorded in 24 per cent of the control group. This figure is difficult to record, because of the variable findings of the examiners. Of the Aureomycin treated group, enlargement of the spleen was absent in 66 per cent of the cases, and in those cases which received Aureomycin within the first ten days of the disease, 80 per cent remained free of splenomegaly. Two cases had an enlarged spleen before therapy with Aureomycin was instituted. No data is available concerning whether the spleen size decreased due to therapy.

Liver Involvement: Liver involvement occurred in 71 per cent of the control group, and in 75 per cent of the entire Aureomycin group, and in 67 per cent of the group receiving Aureomycin in the first ten days of the disease. However, the duration of hepatic involvement as determined by the usual laboratory tests for liver function is quite different for the two groups. In the control group, duration of abnormal liver function averaged seventy-six days with a maximum of 149 and a minimum of thirty-five days. In the Aureomycin treated group the average was twenty-nine days, and for those receiving Aureomycin in the first ten days of the disease, twenty-seven days.

Symptoms: Complete disappearance of symptoms within forty-eight hours or less occurred in the majority of cases and frequently within as little as six hours. In general the disappearance of malaise and other systemic symptoms paralleled the return of temperature to normal. Also, the post-infectious asthenia was considerably less in those patients who received Aureomycin.

Summary and Conclusions: From the data given above, although limited for so protean a disease as infectious mononucleosis, Aureomycin can be concluded to be effective in decreasing duration of fever, hospital stay, and total course of the disease by clinical measures. The subjective response in relief of symptoms within twenty-four to forty-eight hours also was very striking, although it cannot be evaluated in figures. It is felt that the duration of liver involvement is definitely reduced by Aureomycin therapy, as seen in a return to normal of the laboratory tests within approximately 36 per cent of the duration of the hepatic involvement in the control group.

The development of heterophile agglutination titre may be prevented to some extent by treating the disease early with Aureomycin. The abnormal blood picture and the atypical lymphocytosis apparently is not influenced by the drug.

This study is being developed further to include a larger number of cases, and also with attention to recurrence in control and Aureomycin treated cases.

The Diagnostic Value of Urinary Pepsinogen Excretion in Diseases of the Upper Gastrointestinal Tract

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The excretion of urinary pepsinogen may have diagnostic significance in disorders of the upper gastrointestinal tract since patients with active duodenal ulceration excrete, on the average, four times as much urinary pepsinogen as do subjects without ulcer. Urinary pepsinogen (uropepsin), the proteolytic enzyme of urine which is active in the acid range of pH, originates from the gastric mucous membrane and is probably identical with gastric pepsinogen. The pro-enzyme contained in the peptic cells is partitioned into exocrine and endocrine fractions. The major portion, secreted into the gastric lumen, is converted to pepsin in the presence of HCl, in which form it cannot undergo gastrointestinal absorption. The smaller fraction of pepsinogen which diffuses into the tissue fluid enters the blood and is excreted in the urine as such.

We have measured the urinary pepsinogen excretion in 82 individuals, with and without upper gastrointestinal disorders, by means of Mirsky's modification of the Anson-Mirsky-Bucher method for estimating pepsin activity, using lyophilized bovine hemoglobin for the substrate as reported from this Laboratory. Measurements were made on urines collected for periods of 3 to 12 hours, either with the patient in the fasting state or 5 to 8 hours postprandially. A unit of uropepsin has been defined as the amount of enzyme which releases 1 x 10^{-4} mEq. of tyrosine from the hemoglobin substrate in 10 minutes at 37° C.; the present results have been expressed as units of uropepsin excreted per hour (U/hr.).

The 82 patients fell into six clinical categories, characterized as follows: (a) No gastrointestinal complaints nor demonstrable disease of the digestive tract (controls); (b) clinically active duodenal or marginal ulceration, confirmed by roentgen examination or at operation; (c) proven benign gastric ulcer; (d) malignant gastric neoplasms; (e) achylia gastrica of Addisonian pernicious anemia; and (f) total gastrectomy. The range of uropepsin excretion and the mean for each of these groups are as follows:

	No. of cases	*Range*	*Mean*	*(S.D.$_m$)*
(a) Controls	34	0-131	44	(± 6)
(b) Duodenal or marginal ulcer	31	115-373	187	(± 13)
(c) Gastric ulcer	4	43-125	87	
(d) Neoplasm	6	0-112	57	
(e) Pernicious anemia	6	0	0	
(f) Gastrectomy	1	0	0	

Ninety-four per cent (32) of the control group excreted less than 100 U/hr.; 97 per cent (30) of the subjects with duodenal or stomal ulceration put out more than 120 U/hr. In spite of the overlap of the ranges of these two groups, the difference between their means is statistically significant ($t=9.59$, $n=63$, $P<.0001$). The gastric ulcer and carcinoma groups, although they are small, both fall within the range for the control values. The last two groups represent patients incapable of elaborating gastric pepsinogen, and this is reflected by their failure to excrete uropepsin.

In view of the difference in excretion of pepsinogen in the duodenal and stomal ulcer group as compared with the non-ulcer group, this method appears to have diagnostic value, especially in subjects with gastrointestinal bleeding where other diagnostic procedures must be held in abeyance.

Bacteriologic and Epidemiologic Approach to the Treatment of Respiratory Infections With Aerosols of Specific Antibiotics

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In the treatment of sino-respiratory infection with penicillin aerosols, it was found that not all patients responded to this antibiotic. It was reasoned that failures were due in part to the presence of organisms not sensitive to penicillin. It was also noted that even after an excellent response to penicillin there were frequently early recurrences, particularly in children. In searching for the explanation of these repeated or continuous infections, despite treatment, the possibility of carrier states was considered, since it was frequently necessary to treat several members of the same family. A bacteriologic and epidemiologic investigation was, therefore, made of patients, and in selected instances of two or more members of a family.

For the purpose of expedience, cultures were limited to the pharynx; 163 patients were examined, and 225 cultures obtained in which 583 isolates were harvested. 563 of these isolates were exposed to the antibacterial action of penicillin, streptomycin and bacitracin. As aureomycin and chloromycetin became available, these were used in addition to the other antibiotics, so that 164 isolates obtained in 69 cultures were tested as well with all of the common potent antibiotics. The results are summarized in the following tables:—

TABLE I—CLASSIFICATION AND FREQUENCY OF 583 ISOLATES OBTAINED BY PHARYNGEAL CULTURES OF 163 PATIENTS

Organisms	*No. of Times Cultured*	*% of Frequency*
Streptococci:		
Alpha hemolytic	7	1.2
Beta hemolytic	39	6.6
Non-hemolytic	137	23.5
Straphylococci:		
Hemolytic (alpha & beta)	55	9.4
Non-hemolytic	104	17.8
N. Catarrhalis	110	18.8
Pneumococci	59	10.1
Proteus Vulgaris	29	4.9
Diphtheroids	16	2.7
Coliform Bacilli	9	1.5
Tetragenous	8	1.3
Friedländer Bacilus	6	1.0
Streptobacilli	2	0.3
Micrococci	2	0.3

TABLE II — INHIBITORY* ACTION OF PENICILLIN, BACITRACIN AND STREPTOMYCIN AGAINST 564 ISOLATES OBTAINED BY PHARYNGEAL CULTURE

Inhibitory Action	*No. of Organisms*	*%*
Penicillin only	7	1.2
Streptomycin only	37	6.5
Bacitracin only	10	1.7
Penicillin and not by Bacitracin	68	12.0
Bacitracin and not by Penicillin	64	11.3
Equally by Penicillin and Bacitracin	369	65.4
Bacitracin and not by Streptomycin	75	13.3
Penicillin and not by Streptomycin	73	13.1
Equally by Bacitracin and Streptomycin	361	64.0
Equally by Penicillin, Streptomycin and Bacitracin	305	54.0
Not inhibited by either Penicillin, Bacitracin or Streptomycin	20	3.5

* Concentration of antibiotic/cc in final broth dilution for inhibition studies were:

Penicillin— 1 unit
Bacitracin— 10 gamma
Streptomycin— 10 "

TABLE III — INHIBITORY* ACTION OF PENICILLIN, BACITRACIN, STREPTOMYCIN, AUREOMYCIN AND CHLOROMYCETIN (CHLORAMPHENICOL) AGAINST 164 ISOLATES OBTAINED BY PHARYNGEAL CULTURE

Inhibitory Action	*No. of Organisms*	*%*
Aureomycin	130	79.2
Chloromycetin (Chloramphenicol)	62	37.8
Penicillin	122	74.4
Streptomycin	121	73.7
Bacitracin	138	84.1
Aureomycin only	5	3.0
Chloromycetin only	0	0.
Penicillin only	1	0.6
Streptomycin only	6	3.6
Bacitracin only	2	1.2
Not inhibited by any antibiotics	3	1.8

* Concentration of antibiotic/cc in final broth dilution for inhibition studies were:

Penicillin— 1 unit
Bacitracin— 10 gamma
Streptomycin— 10 "
Aureomycin— 10 "
Chloromycetin— 10 "

SUMMARY AND CONCLUSIONS:

Pharyngeal cultures (225) obtained from 163 patients suffering from sino-respiratory infection netted 583 isolates; 564 of these were subjected to the inhibitory action of penicillin, bacitracin and streptomycin; 164 isolates were similarly treated and, in addition, tested with aureomycin and chloromycetin. Of the newer antibiotics, bacitracin and aureomycin proved to be highly efficient. Chloromycetin exerted relatively poor inhibitory action compared with these, or with penicillin or streptomycin.

No inhibitory action of any of these five antibiotics was noted against 3 organisms (1.8 per cent), nor against 20 organisms (3.5 per cent), when only penicillin, bacitracin or streptomycin were employed.

These facts indicate the value of culture and inhibitory tests as a guide to therapy.

In the contagious aspect of this study, forty-three people in seventeen family units were cultured 68 times, and 159 organisms isolated and identified. These studies reveal the possibility of the existence of a carrier state in ten of the seventeen families studied. This may account for repeated reinfection, or for chronic infection of the sino-respiratory tract as seen in practice.

TABLE IV—EVALUATION OF POSSIBLE EPIDEMIOLOGIC RELATIONSHIP OF 159 ISOLATES OBTAINED FROM 68 CULTURES IN 17 FAMILIES

No.	*Family*	*No. of Members of Family Cultured*	*Complete*	*Incomplete*	*No. of Patients with Pathologic Organisms*	*Possible Contagion*	*Pathologic Organism Involved*
1	*Sha.*	4	#		3	+	Hemol. Staph
2	*Mol.*	3		#	2	+	Hemol. Staph.
3	*Sch.*	2		#	0	—	None
4	*Mor.*	2		#	0	—	None
5	*Gol.*	3	#		2	+	Beta Hemol. Staph. & Diphtheroids
6	*Kam.*	2		#	2	+	Beta Hemol. Strep.
7	*Dem.*	2		#	0	—	None
8	*Blu.*	2	#		0	—	None
9	*Gow.*	3		#	0	—	None
10	*God.*	2	#		2	+	Pneumococci
11	*Sei.*	2		#	0	—	None
12	*Leo.*	2		#	2	+	Pneumococci
13	*Amb.*	3	#		2	+	Pneumococci
14	*Was.*	3		#	2	+	Hemol. Strep. & Pneumococci
15	*Tos.*	3		#	3	+	Pneumococci
16	*Coh.*	3	#		3	+	Pneumococci
17	*Sol.*	2		#	0	—	None
17		43	6	11	23	10	

The Effects of Experimental Acidosis on the Dynamics of the Circulation

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Acidosis of the blood was produced in six dogs under artificial respiration by giving intravenous infusions of gluconic acid or acid sodium phosphate. The pH of the blood was thus lowered in steps and the behavior of the circulation investigated under these conditions. Acidosis within the range seen in diabetes and uremia produces a marked reduction in peripheral resistance which may decrease up to a fourth of its original value. Until very marked lowering of the pH is achieved, the mean blood pressure, taken with the Sanborn Electromanometer from the femoral artery, remains essentially constant. The minute output, determined according to Fick's principle by cardiac catheterization, increases up to three times its basic value. Since the pulse rate decreases slightly under acidification the stroke volume is increased still more markedly. As a consequence of the peripheral dilatation, the pulse pressure widens considerably. The venous pressure remains normal until extreme lowering of the pH to values of 6.8 or below is produced. When such severe acidosis is induced, the heart is unable to compensate for the further reduction in peripheral resistance, the blood pressure falls rapidly and the animal dies in a shock-like picture.

Generalized vasoconstriction produced in three dogs by induction of hypothermia can be relieved by lowering the pH of the blood.

The ability of the heart to increase its output to such an extent for considerable length of time without failing may be due to the increased oxygen dissociation accompanying acidosis.

These findings explain part of the circulatory phenomena, as seen in diabetic and uremic acidosis and coma, which so far were attributed mostly to dehydration.

The Adductor Longus Syndrome: A Cause of Groin Pain; Its Treatment by Local Block of Trigger Areas (Procaine Infiltration and Ethyl Chloride Spray)

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In 50 patients with groin pain, the immediate source of this complaint was traced to trigger areas in the adductor longus muscle. Spasm and tenderness of this muscle were demonstrable. Pain referred from the upper third or half of the adductor longus was perceived deep in the groin, whereas the pain reference from its lower part extended also downward over the anteromedial aspect of the thigh and knee and at times over the pretibial region as far as the ankle. The pattern of pain reference was relatively constant from person to person, and was clearly demonstrated in these subjects by mechanical stimulation of the trigger areas at these sites, either by means of digital palpation or insertion of the needle within the muscle mass at the time of procaine infiltration.

Uniformly good results were obtained by local measures which block somatic trigger mechanisms. In most of the patients the trigger areas were infiltrated with a 0.5 per cent solution of procaine hydrochloride in

physiologic saline. In many instances, ethyl chloride spray was also used. The spray was lightly applied over the adductor longus muscle and groin in rhythmic upward sweeps in such a manner that frosting and cold pain were avoided. Gentle passive stretch was exerted on the muscle during spraying. In one patient, reported as "allergic" to procaine, groin pain was relieved by infiltration of the trigger areas with physiologic saline. In five patients, permanent relief of pain was secured by repeated (daily) application of the spray alone; in these subjects, the limitation of adduction of the thigh resulting from spasm of the adductor longus muscle, was seen to diminish or disappear at once, that is, during application of the spray. In other cases, when the spray produced no objective relaxation of this muscle, procaine infiltration was usually carried out immediately.

Relief of groin pain was permanent when spasm of the adductor longus muscle was caused by direct injury. When the spasm developed reflexly as the result of remote organic disease, relief of pain was usually temporary owing to constant reactivation of the vicious cycle of spasm-pain-spasm. Even in the latter group, which included 4 patients with metastatic carcinoma of the lumbar spine and pelvis and 4 patients with osteoarthritis of the hip joint, symptomatic relief was regarded by the patient as satisfactory. In osteoarthritis of the hip joint, instantaneous relief of nocturnal referred pain was obtained by the patient's applying the spray briefly whenever necessary during the night.

Thus, when muscular pain is relieved by such measures which block trigger mechanisms, no deductions can be drawn from that fact alone as to the primary cause of pain. It is only with the passage of time and further study of the patient that the differentiation can be made between a *physiologic* disorder of the myofascial tissues and a reflex cycle activated by remote *pathologic* lesions.

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